REMARKS

Amendments to the Specification

Applicants have amended the specification and the abstract to address the Examiner objections.

Claims Status

Claims 1 – 17 are pending. Claims 1 – 10 have been rejected. Claims 1 – 5, and 8 are being amended. Claims 11 – 17 are new. Claims 3, 4, and 5 have been rewritten to depend only from claim 1 as opposed to either claim 1 or claim 2. Thus, claims 11 – 17 are newly added dependent claims that depend from independent claim 2. No new matter is introduced by these amendments.

Reconsideration is respectfully requested.

Claim Rejections - 35 USC § 112

The Examiner has rejected claim 8 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants believe that amendment to claim 8 addresses the Examiner's rejection.

Claim Rejections - 35 USC § 103

The Examiner has rejected claims 1 – 10 under 35 U.S.C. § 103(a) as being unpatentable over Leonard et al., European Patent No. 1 382 337 A1 (Leonard), further in view of Conte et al., United States Patent No. 5,422,123 (Conte), Chen et al.,

United States Patent No. 6,720,003 B2 (Chen), and Lowey, United States Patent No. 4,775,535 (Lowey).

The Examiner's Contentions

It is the Examiner's view that Leonard discloses, "a sustained-release tablet for oral administration having a tablet core comprising paroxetine as pharmaceutically active substance, a support platform (partial separation layer), and an outer enteric coating layer." Also, the Examiner points out that Leonard specifically cites Conte "for particularly preferred formulations (Pg. 2, sec. 0019)." The Examiner admits that Leonard and Conte disclose "a support platform that only partially encloses the tablet core and do not specify that the support platform (separation layer) is 1-30 w/w% relative to the tablet core." Further, the Examiner admits that Conte and Leonard do not "disclose the step of further adding low viscosity hydroxypropylmethyl cellulose to the paroxetine-containing granules."

The Examiner then cites Chen for the disclosure of paroxentine tablets manufactured with water soluble polymers that "can be overcoated with a film coating in combination with an enteric coating material." It is the Examiner's view that the film coatings are "equivalent to a separation layer that completely encloses the tablet core." Lowey is cited for disclosing "sustained release formulations for unit dosage forms with substantially uniform and comparable bioavailability characteristics (Col. 2, Ins. 59-68; Col 3, In. 1) using hydroxypropylmethyl cellulose as the preferred carrier base material (Col. 6, Ins 34-35)."

The Examiner then states that Lowey shows that "[f]ormulating enteric coated oral dosage forms with water-soluble and insoluble polymers of the types described is a well established practice in the art (Lowry et al., Col. 1, Ins. 52-63)." The Examiner finds that Applicants invention would have been obvious as one would have been led to "design a sustained-release tablet in which a separation layer completely enclosed a tablet core based on the teachings of Chen et al." With respect to the tablet core formulation the Examiner states that one would have "incorporate[d] the selected ranges of w/w% proportions for the various tablet ingredients and components as described based on the teachings of "Chen and Lowey. Concluding, the Examiner asserts that that one would have had a "reasonable expectation of success in achieving superior sustained-release performance with uniform and comparable bioavailability."

Applicants' Response

Without concurring in the Examiner's analysis and to further clarify what Applicants regard as the invention, claims 1 and 2 have been modified to include the feature "a separation layer that completely encloses the tablet core."

The Examiner has not established a *prima facie* case of obviousness for the following reasons.

First, it has been established that "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)." Manual of Patent Examining Procedure, 8th

Edition, § 2143.01. Thus, the combination of Leonard with Conte by incorporation by reference with Chen and Lowey is impermissible.

As correctly noted by the Examiner, Leonard cites the formulations of Conte as particularly preferred. However, the Examiner notes that the formulation of Conte includes only a partial support, or partial coating, underneath the enteric film coating. Thus, the Examiner has cited the film coatings of Chen, and equated them to Applicants' separation layer. As best understood by Applicants, the Examiner is concluding that one of skill in the art would have entirely coated the core of Conte with the film coating of Chen. However, such modification of Conte and/or Leonard would change the principle of operation.

Conte is directed to a solid oral dosage form with "a core of defined geometrical form" and "a support applied to said core to partly cover its surface, and are characterized in that said support consists of polymer substances which are slowly soluble and/or slowly gellable in aqueous liquids" (column 2, lines 26 – 29). The purpose of the "support" is described in Conte at column 2, line 66 to column 3, line 7 (emphasis added):

> The support has a thickness of between 10 microns and 3-4 mm depending on the hydrophilic characteristics of the components, its task being to limit and define the direction of release of the active substance contained in the cope.
>
> In this respect, as the support is generally less hydrophilic than the core and does not contain active substance, the transfer of active substance can occur to a significant and immediate extent only from that portion of the cope [core] which is not covered by the support.

Therefore, the support is added to limit release to the sides of the tablet core that are uncoated.

The tablets of Leonard are similar as page 3, lines 1 – 8 of the specification disclose a dosage form comprising (a) a deposit core and (b) a support platform wherein the support platform is "an elastic support, applied to the deposit core so that it partially covers the surface of

the deposit core" (emphasis added). As noted by the Examiner, Leonard specifically references the disclosure of Conte.

As the intent of the support layer of Conte, and by reference, Leonard, is to obtain a "constant controlled-rate release of active substances" which is accomplished by limiting the release of active substance to the sides of the tablet core that are uncoated with the support, coating of all sides or the entire surface of the core would be a change in the principle of operation. Therefore, the teachings of Leonard, as modified by Conte, combined with the teachings of Chen, in the manner proposed by the Examiner, is impermissible.

Second, establishing a *prima facie* case of obviousness requires more than citation to references disclosing the individual elements. According to the Supreme Court, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR International Co. v. Teleflex Inc. et al.*, 127 S. Ct. 1727, 1741 (2007). Although a teaching, suggestion, or motivation need not be found in the art, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* (citations omitted).

The Examiner has stated that Applicants' claimed invention would have been obvious to one of skill in the art based upon the disclosures of Lowey and Chen. The Examiner has cited Lowey for the disclosure of formulating with hydroxypropylmethyl cellulose (HPMC). Chen is cited for film coating as well as formulating a sustained release paroxetine tablet. However, Chen and Lowey, either alone or in combination, do not render obvious the particular formulation claimed by Applicants.

Chen does not expressly disclose coating a tablet core with more than one layer. Moreover, Chen's disclosures, "[o]ptionally, the tablets may be overcoated with a pharmaceutically acceptable film-coating, e.g., for aesthetic purposes (e.g., including a colorant), for stability purposes (e.g., coated with a moisture barrier), for taste-masking purposes, etc." (column 10, lines 12 – 17), and "[i]n further embodiments of the present invention, the tablet coating may be comprised of an enteric coating material, alone or in combination with a hydrophobic polymer coating" (column 10, lines 46 – 49), do not render obvious Applicants' claimed invention. Chen merely discloses that the tablets may optionally be coated with any number of coating materials. Lowey only discloses that the tablets may be "coated or uncoated" (column 5, line 46). There is nothing in the disclosure of Lowey or Chen that would have led one to have used two coating layers.

Thus, the teachings of Lowey and Chen, either alone or in combination, does not render obvious a coating completely enclosing the tablet core of a "a mixture of a) at least one water-insoluble polymer selected from the group consisting of ethylcellulose, polyvinylacetate and ammoniomethacrylate copolymer type B and b) at least one water-soluble polymer selected from the group consisting of hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, ammoniomethacrylate copolymer type A and polyvinylalcohol," or " a water-soluble polymer selected from the group consisting of hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, ammoniomethacrylate copolymer type A and polyvinylalcohol" and on top of such coating, an enteric coating. In particular, neither Chen nor Lowey disclose using a mixture of one water insoluble polymer with one water soluble polymer as a coating material. Additionally, neither Lowey nor Chen disclose the particular core tablet formulation, that is use of a combination of

high and low viscosity HPMC intragranularly with paroxetine, and use of a low viscosity HPMC extragranularly.

It appears that the Examiner has taken the position that if one might happen upon Applicants' claimed invention, it is obvious. This is not the test for obviousness. As noted above, the Examiner must provide some "articulated technical reasoning" to explain why one of ordinary skill in art would have arrived at Applicants' claimed invention. In the current case, the Examiner has provided no explanation as to why one would have surrounded the tablet core with the film coating of Chen in addition to the enteric coating. Applicants have provided a specific rationale for the two coating layers that is not disclosed, suggested, or even hinted at in the references cited by the Examiner in rejecting claims 1 – 10. Moreover , the Examiner has not explained why one would have been led to the particular core tablet formulation of Applicants' claimed invention. It is clear that the Examiner is relying upon hindsight to reach the conclusion that Applicants' claimed invention is obvious.

Third, the two coating layers perform a function that is neither disclosed nor suggested in any of the references cited by the Examiner in rejecting claims 1 – 10. Applicants claimed invention is directed to a three-layered tablet consisting of a tablet core, a separation layer and an enteric coating layer. The invention provides an enteric sustained release tablet that maintains a constant drug release without regard to the effect of gastric emptying time (GET). As discussed in the specification, Applicants have found that when an enteric coating layer is directly introduced on a sustained release tablet core containing paroxetine, the release behavior of the tablet significantly changes and they found that such release behavior of the tablet is largely subject to GET. That is, it was found that drug release behavior of such tablet varies if it has been previously exposed to acidic conditions such as the acid of the stomach (see paragraph

[0006] of the published application, US2008/0292696). The function of the two coating layers, the separation layer and enteric coating layer, is to allow the sustained release of paroxetine as designed once the tablet reaches intestine without regard to the GET, and such function is not suggested or disclosed by Lowey, Chen, Leonard or Conte. The above cited references do not disclose any impact of GET on the drug release rates, and do not disclose the impact of pH on drug release rates. Thus, the two layers allow the dosage form to perform a function that would not have been predicted by these references.

In summary, for all of the reasons cited above, the Examiner has not established a *prima facie* case of obviousness of claims 1 and 2. Thus, there is no *prima facie* case for obviousness of the claims that depend from claims 1 or 2, claims 3 – 17. Applicants request the withdrawal of the rejections and allowance of claims 1 – 17.

Patentability of New Claims

Claims 3, 4 and 5 have been amended to depend from claim 1 rather than claim 1 or claim 2. New claims 11 – 17 are new dependent claims that depend from claim 2 and cover part of the same subject matter as prior multiple dependent claims 3, 4, and 5, and claims 6, 7, 8, and 10 which depend from claim 5. Thus, the subject matter of these new claims has already been examined.

As the patentability of claim 2 is discussed above, the new claims 11 – 17 are patentable for at least the same reason that claim 2 is patentable.

Conclusion

In light of the foregoing claim amendments and remarks, this application is considered to be in condition for allowance. Applicants respectfully request the allowance of pending claims 1 – 17.

If necessary to ensure a timely response, this paper should be considered as a petition for an Extension of Time sufficient to provide a timely response. The undersigned authorizes the Commissioner to charge any fees that may be required, or credit of any overpayment to be made, to **Squire, Sanders, and Dempsey Deposit Account No. 07-1850**.

Should the Examiner have any questions regarding this communication, the Examiner is invited to contact the undersigned at the telephone number shown below.

Respectfully submitted,

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